

<b>PRE-APPEAL BRIEF REQUEST FOR REVIEW</b>		Docket Number (Optional) <div style="text-align: center;">223002107100</div>	
	Application Number	Filed	
	10/762,873	January 21, 2004	
	First Named Inventor		
	Nicholas M. VALIANTE, Jr.		
	1617	Examiner <div style="text-align: center;">Y. S. Chong</div>	
<p>Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.</p> <p>This request is being filed with a notice of appeal. A Final Office Action was mailed 06 October 2008 and a Notice of Appeal is therefore due 06 April 2009.</p> <p>The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided.</p> <p>I am the</p> <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="width: 60%;"> <p><input type="checkbox"/> applicant /inventor.</p> <p><input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)</p> <p><input checked="" type="checkbox"/> attorney or agent of record. Registration number <u>44,422</u></p> <p><input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____</p> </div> <div style="width: 35%; text-align: center;"> <p>_____ /Michael G. Smith/ Signature</p> <p>_____ Michael G. Smith Typed or printed name</p> <p>_____ (858) 702-5113 Telephone number</p> <p>_____ April 6, 2009 Date</p> </div> </div> <p><small>NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.</small></p>			
<input checked="" type="checkbox"/> *Total of <u>1</u> forms are submitted.			

### Pre-Appeal Brief Request for Review

The claims at issue encompass immunogenic pharmaceutical compositions comprising an antigen and a ‘tryptanthrin compound adjuvant’ that acts as an adjuvant to promote antigenic response to the antigen in the composition. (As there seems to be some confusion about the term ‘adjuvant’, Applicants note that a “tryptanthrin compound adjuvant” as used in the claims does not describe a tryptanthrin compound *plus* an adjuvant, but a tryptanthrin compound *acting as an adjuvant* in the claimed immunogenic composition. See specification at, e.g., paragraph [014].) Claims 12-17 and 19 are under final rejection. The outstanding rejections are for obviousness over Baker et al. (U.S. Patent 5,441,955) in view of Colston et al. (U.S. Patent 7,122,195). Applicants believe the rejections are improper, and request review for the following reasons:

Reason 1. The Examiner has not established a *prima facie* case of obviousness because the proposed combination would have been expected to be inoperative.

Baker discloses its tryptanthrin compounds as antibacterial agents, useful for treating bacterial infections and killing mycobacteria in particular. See Baker, col. 1, lines 7-14: “The present invention relates to new indolo[2,1-b]quinazoline-6,12-dione derivatives which are useful in killing mycobacteria....” The Examiner proposed combining BCG vaccine, which is not disclosed or suggested by Baker, with a tryptanthrin compound to form a hypothetical composition that allegedly provides a *prima facie* case of obviousness.

Colston’s compositions comprise a live mycobacterium as an immune response potentiator, combined with an antigen selected to provide immunity to a desired organism. The persistence of the live mycobacterium in the host without causing an aggressive infection is necessary for the composition to work. See Colston, col. 2, lines 45-48: “The ability of BCG to survive for prolonged periods without causing progressive infection in immunocompetent individuals is an important component of its protective properties.”

Baker’s statement anti-mycobacterial compounds would have been expected to inactivate Colston’s mycobacterium-dependent vaccine composition if the two were mixed together, rendering the composition ineffective. One of ordinary skill would have had neither a motivation to combine Baker’s compounds with Colston’s vaccine, nor a reasonable expectation that the combination would be effective. Baker’s teaching that its compounds are useful in killing mycobacteria provides

a clear, if implicit, *teaching away* from mixing it with Colston's vaccines or BCG, both of which use a *live* mycobacterium. Because the combination of Baker's compounds with the vaccine composition of Colston would be expected to render the vaccine unsuitable for its intended use, combining these references in an obviousness rejection is improper. See MPEP 2143.01(V) ("The proposed modification cannot render the prior art unsatisfactory for its intended purpose.")

Because the person of ordinary skill would NOT have had motivation to combine Baker's compounds with Colston's vaccine, or an expectation of success when doing so, the two references do not support a *prima facie* case for obviousness. The obviousness rejection based on Baker and Colston is overcome and should be withdrawn.

Reason 2. The Examiner improperly ignored factors that a person of ordinary skill in the art would have considered before mixing Baker's compound with Colston's vaccine.

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." In the present case, no real reason for combining the Baker compounds with the Colston compositions was provided, and no advantage of mixing them together was identified. The Examiner relied on a statement in Baker saying its compounds can be used 'in combination with' other active agents, exemplified by several antibiotics, and cited *In re Kerkhoven*. The cited portion of Baker does not disclose or suggest that the other agent should be mixed with Baker's compound, nor does it say the other active agent could be a vaccine. No rationale was provided to explain why this general statement would lead one of ordinary skill to combine Baker's compounds into a single composition with Colston's vaccines. The justification for combining them rested largely on *In re Kerkhoven*: "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...The idea of combining them flows logically from their having been individually taught in the prior art."

In *Kerkhoven*, the Court noted that the combination required "no more than the mixing together of two conventional spray-dried detergents." Here, the antibacterials of Baker and the vaccines of Colston operate by quite different mechanisms and target different patient populations, a vaccine being primarily preventive, while an antibacterial is ordinarily used as a

treatment. The two categories are well known to require different formulations and administration routes and schedules. Mixing them together is entirely unlike mixing the detergents in *Kerkhoven*. One of ordinary skill knows this, and would not have been motivated to mix together an antibiotic and a vaccine without some expected advantage: the Examiner has identified *no expected advantages* provided by the mixture, and those skilled in the art know would not consider mixing pharmaceuticals together like mixing detergents.

While admitting that drug interactions are a “general concern for anyone in the medical field” the Examiner ignores this factor in the obviousness analysis because “it would apply to any drug combination.” That is *improper*, though, since such recognized interactions are *precisely* the kind of issue a person of ordinary skill would *necessarily* consider before mixing a vaccine with an antibiotic. The Examiner ignores evidence that teaches against the combination by arguing that the user could administer the combination once, then administer the antibiotic separately, since the claims use the open transitional language ‘comprising’. But this misses the point: there is no reason to mix them together for even one administration, and many reasons *not* to.

The Examiner rejects as unpersuasive arguments that antibiotic compounds and vaccines act by vastly different mechanisms and are not ordinarily combined. The Examiner states that “there are many combination therapies in the medical field that work via different or multiple mechanisms of action. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in treating pathogenic mycobacterial infections by administering tryptanthrin with an adjuvant because of the therapeutically additive effect of combining two known active agents for the same purpose.” That argument is unpersuasive, though, because the Examiner has provided no examples or evidence to suggest that a person of ordinary skill would consider it normal or reasonable to combine an antibacterial with a vaccine.

The Examiner also disregarded a reference provided by the Applicants suggesting that combining a vaccine with an antibiotic tends to reduce their effectiveness, because “the reference does not state that the combination of vaccines and antibiotics will not work, but that the combination will be less effective.” This already demonstrates that the rationale of providing them to provide ‘additive effects’: that is not the expected result. Even if the cited references suggested concurrent *use* of the tryptanthrin compounds with a vaccine, that does not disclose, suggest or require mixing them into a single composition for an obviousness rejection. In the absence of *any*

recognized advantage provided by the combination, the evidence above, which the Examiner admits provides a reason to expect the combination to be less active than the separate treatments, rebuts any conclusion that it would have been obvious to combine the teachings of the references. A conclusion of obviousness is inappropriate, because the evidence would have left a person of ordinary skill with un rebutted reasons NOT to combine the reference teachings.

The Examiner has recognized that the art teaches disadvantages of concurrent *usage* of a vaccine and an antibiotic, which seems to make *mixing them together* really inappropriate, but maintains one of ordinary skill would nonetheless have *mixed* the Baker antibacterial with the Colston vaccine, apparently based only on *Kerkhoven*. The Applicants respectfully assert that *Kerkhoven* provides no reason to mix a vaccine with an antibacterial where teachings in the art suggest that a vaccine will generally reduce the effectiveness of any antibacterial, which already distinguishes this clearly from *Kerkhoven's* facts. And in this particular case, the *particular* antibacterial would be expected to inactivate the *particular* vaccine, further distinguishing *Kerkhoven*. Post-KSR, the Office still requires a reason to combine reference teachings. In this case, none has been provided, while the record shows that a person of ordinary skill had several reasons not to do so. These facts do not provide a *prima facie* case of obviousness, because the person of ordinary skill had no reason to make the combination proposed by the Examiner, and every reason to doubt that such a combination would be effective.

3. Even if *prima facie* obviousness were shown, the unexpected immune-enhancing effect of the tryptanthrin compounds rebuts a conclusion of obviousness.

Because a *prima facie* case of obviousness has not been established, Applicants have no burden to provide rebuttal evidence. Nevertheless, the record provides evidence rebutting a conclusion of obviousness. The specification demonstrates that the tryptanthrin compounds produce an unexpected immune-stimulating response in the claimed compositions. The Valiante Declaration shows that combining a tryptanthrin compounds with an antigen enhances the antigenic effect of the antigen. These effects could not have been expected from the prior art, which discloses only antibacterial activity for the tryptanthrin compounds.

The Examiner rejected this evidence, saying, "Examiner does not view this as unexpected properties since tryptanthrin is a known compound." Applicants note that the inherent properties of a known compound are not themselves known, and cannot be relied upon to support a conclusion of

obviousness. MPEP 2141.02(V): “Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).” The inherent properties of the tryptanthrin compounds that are the subject of the present invention—their ability to promote an enhanced immune response to an antigen—would not have been expected.

The determination of obviousness or nonobviousness must be made in view of all of the evidence of record. When rebuttal evidence is presented for an alleged *prima facie* case of obviousness, the Examiner must consider all of the evidence before arriving at an ultimate conclusion. MPEP 2145. Because the application and declaration provide evidence of an unexpected effect, a conclusion that the claimed invention would have been obvious is rebutted.

The combination of Baker’s compounds with Colston’s vaccines would not be expected to work because of the anti-mycobacterial activity of Baker’s compounds. That alone destroys the alleged *prima facie* case of obviousness. Applicants have shown that mixing pharmaceutical agents raises concerns about drug interactions, and have provided evidence that combining an antibiotic with a vaccine is expected to reduce the vaccine’s effectiveness and is not customary in the art. All of this evidence stands unrebutted. For pharmaceutical arts generally, and for vaccines in particular, these facts distinguish mixing agents together in this art from mixing the detergents in *Kerkhoven*. Finally, the immune enhancing activity of the claimed compositions provides an unexpected result, which was not known or suggested by the prior art, and rebuts a conclusion of obviousness. Even if a *prima facie* case for obviousness were established, it would be overcome by the unrebutted evidence favoring a conclusion of nonobviousness.

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Respectfully submitted,

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